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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/020,478	12/13/2001	C. Frank Bennett	RTS-0303	6796

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/020,478	BENNETT ET AL.DR	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9-7-04 & 12/13/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communications filed 10-19-04 and 10-5-04.

Claims 1, 2, 4-20 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The declarations under 37 CFR 1.132 filed 10-5-04 and 10-19-04 are insufficient to overcome the rejections of record for the reasons elaborated below in addressing arguments for the maintained rejections (see response to arguments addressing the 103 rejection below).

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro inhibition of expression of SEQ ID NO: 3, does not reasonably provide enablement for the in vivo targeting and inhibition of SEQ ID NO; 3, nor for treatment in an organism comprising the administration of antisense targeting SEQ ID NO: 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and/or use the invention commensurate in scope with these claims for the same reasons of record as set forth in the Office action mailed 5-5-04.

Applicant's arguments filed 10-5-04 have been fully considered but they are not persuasive. Applicants argue that the scope of the invention claimed is fully enabled and that none of the cited references (e.g. of Crooke, Branch, Palu, Tamm, Agrawal and Chirila) support the position taken by in the Office action mailed 5-5-04 that the scope claimed lacks enablement. Applicants argue, for instance, that the Branch reference does not teach that such barriers as target accessibility and delivery of antisense are not insurmountable. Applicants argue further that the Crooke reference teaches that in vivo administration of antisense compounds would be expected to have at least some activity in vivo, that the Tamm reference was taken out of context, and that the Palu reference is completely irrelevant. Contrary to Applicants' assertions, the references of Crooke, Branch, Palu, Tamm, Agrawal, Chirilla, etc have been properly relied upon to support the enablement rejection of record. Chirila, for instance, states unambiguously that antisense is still an unpredictable endeavor: "Regardless of the precise mechanism of action, which is still a matter of conjecture from case to case, **the advances in AS strategy are afflicted by major problems**. While significant progress has been lately recorded toward solving some of these problems... **there remains a predominant challenge**: the ability to suitably delivery the ODNs in order to assure maximum cellular permeability, effective internalization, and improved efficiency in reaching the target." (see bridging paragraph, pp. 324-325 of Chirila, emphasis added). Chirila reiterates this sentiment of unpredictable delivery of antisense oligonucleotides in other parts of the

publication: "However, the adequate delivery of antisense oligodeoxynucleotides to individual cells **remains an important and inordinately difficult challenge**." (see Chirila, abstract on p. 321, emphasis added).

In further support of the unpredictability of antisense in vivo, Branch states that "...the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target – often through an entirely unexpected mechanism. Non-antisense effects are not necessarily bad... However, their **unpredictability confounds research applications of nucleic acid reagents**." (see Branch, center column of text, p. 45, emphasis added). Branch further elaborates other ways that antisense act unpredictably: "Non-antisense effects are not the only impediments to rational antisense drug design. The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules." (see Branch, bridging paragraph of center and right hand columns, p. 45).

Consistent with this recurring conclusion of antisense unpredictability in the literature, Tamm, in the concluding remarks of the publication, states the following: " Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing... However, if this goal is achieved without a clear proof of principle, the major dilemma of antisense is still unresolved. The beauty and future potential of antisense depends on the design of multiple drugs based on our increasing knowledge of genes and their function. **Only if the therapeutic activity of an**

antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable, will the future for antisense-based drugs become bright. Otherwise, even if particular antisense oligonucleotides become established for systemic treatment of cancer, antisense will not be better than other drug development strategies, most of which depend on an empirical approach." (See final paragraph of Tamm, p. 495, emphasis added).

Contrary to Applicants' assertions, the references cited in the Office action mailed 5-5-04 uniformly reiterate the theme of antisense unpredictability. And this theme is not relegated to a single sentence of a single publication as suggested by Applicant's representative. In addition, Palu had been cited to show that nucleic acid delivery to intended target cells is a limiting factor in vivo generally, and occurs with antisense as well as other forms of nucleic acid therapy approaches. The limitation of adequate delivery of nucleic acids to target cells has been illustrated in the other references, as discussed above.

Applicants also argue that the successful Phase 3 clinical trials for Genasense illustrate that antisense is no longer an unpredictable endeavor to treatment approaches. Contrary to Applicants' assertions, the success of a particular antisense to target a particular target gene and provide treatment effects in an organism is not predictive of the ability to provide target gene inhibition and treatment effects for a different antisense, directed to a different target gene and harbored in a different target cell, and associated with a different condition or disease. The success for each

antisense targeting each target gene must be tested empirically for its ability to inhibit expression in an organism and provide treatment effects.

Applicants argue further that the Chirila reference and the instant disclosure suggest various methods and compounds that can be used to enhance cellular uptake and to utilize these suggestions would not take undue experimentation for in vivo applications. Contrary to Applicants' assertions, the general description of compounds or reagents that can be used to potentially enhance cellular delivery does not substitute for the necessity of providing adequate delivery of a potentially therapeutic agent. A laundry list of commercially available reagents does not render the need for assuring adequate delivery in vivo fulfilled. Contrary to Applicants' assertions, it requires undue experimentation beyond the prophetic disclosures provided in the instant specification, and beyond the mention of available reagents in the literature, to render the invention enabled over the broad scope claimed. The in vitro targeting and inhibition of expression of the target B-cell associated protein gene is not representative or correlative of the ability to treat or prevent any disease or condition associated with the expression of B-cell associated protein, nor is it correlative or representative of the ability to treat or prevent any condition characterized by altered levels of apoptosis or hyperproliferation of cells. No in vivo targeting and inhibition of expression of B-cell associated protein gene has been shown in the instant disclosure, nor any treatment effects. The in vitro experiments are not representative of in vivo target gene inhibition. Therefore, the instant rejection for lacking enablement over the scope claimed is maintained.

Applicants argue on the one hand, regarding the 103 rejection, that "It is not acceptable to extrapolate results obtained for oligomeric compounds targeted to a particular gene to the results that would be reasonably expected for a different set of oligomeric compounds targeted to a different gene." (See declaration filed, 10-19-04, page 3, paragraph 8), and on the other hand, that the results obtained for one antisense in vivo is evidence that in vivo targeting of antisense to another target gene is extrapolatable (see arguments filed 10-5-04, pp. 9-16, esp. pp. 15-16). It appears that Applicants' arguments addressing the enablement rejection directly contradict those which address the obviousness rejection. Contrary to Applicants' assertions, the success obtained for various antisense cited in other studies (e.g. by Smith for bcl-2, Dwyer for c-raf-1, Wang for mdm-2...) is not representative of the ability to successfully deliver antisense and provide treatment effects in vivo using the instantly claimed antisense. Each target gene and antisense represents a different and unpredictable challenge for in vivo application, and the prophetic disclosures of the instant specification do not substitute for the ability to achieve in vivo targeting, inhibition and treatment effects experimentally. Therefore, the instant rejection for lacking enablement is maintained.

Claims 1, 2, 4-15are rejected under 35 U.S.C. 103(a) as being unpatentable over Montano et al in view of Milner et al and McKay claims for the same reasons of record set forth in the Office action mailed 5-5-04.

Applicants argue in the declaration filed 10-19-04 and 10-5-04 that the 103 rejection is improper because the motivation has not been established to render the instant invention obvious and that no reasonable expectation of success has been established to inhibit the target B-cell associated protein gene using antisense in vitro. Contrary to Applicants' assertions, however, antisense inhibition of a known target gene is a routine approach utilized by one of ordinary skill to study the role of a target gene in a cellular process, aberration or cellular participation in a disease state. Montano taught the role of the claimed target gene in developmental processes, tumor suppression and senescence, as well as in determining the sensitivity of estrogen target cells, which cells include breast cancer cells. Montano also taught the polynucleotide sequence of the claimed target gene, from which antisense are derived and assessed for inhibitory capability using routine methods in the field of biochemistry and molecular biology - such as those techniques taught by Milner and McKay for inhibiting the expression of target gene of known nucleotide sequence in vitro. Montano therefore properly taught the motivation to study the role of B-cell associated protein expression in cellular processes, including those involved in tumor suppression and developmental processes of cells. The teachings of Montano, combined with the routine use of antisense oligonucleotides for inhibiting target gene expression, render the instant invention obvious to one of ordinary skill in the art of molecular biology (see Milner at 537, who teaches a combinatorial technique that allows simultaneous assessment of all possible oligonucleotides within a given region to identify sequences open to duplex formation and antisense inhibition of target gene expression: "...the arrays provide a simple

empirical method of selecting effective antisense oligonucleotides for any RNA target of known sequence." render the instant invention obvious). This disclosure, combined with the teachings of Milner in disclosing the routine empirical screening of antisense for their ability to inhibit the translation of any RNA target, render the instant invention obvious (e.g. see the abstract of Milner on page 537).

Applicants declaration and arguments also assert that a subset of oligonucleotides tested either by Milner, or those provided in the oligonucleotide array disclosed in the declarations filed 10-5-04 and 10-19-04, suggest that a reasonable expectation of finding oligonucleotides able to inhibit target gene expression by at least 42% is low, and that finding successful oligonucleotides inhibiting target gene expression to this degree requires more than routine experimentation. It is unclear how the two examples provided in the declarations filed 10-5-04 and 10-19-04 (of antisense inhibition of two unrelated target genes, human tyrosine kinase, non-receptor and rat urate anion exchanger 1 mRNA) are generally representative of an expectation of success of antisense inhbition of target genes, especially in light of the myriad of target genes whose expression is known to be inhibited successfully using antisense (see Tables 12 & 14 from USPN 5,959,096, Tables 1 & 2 from USPN 5,959,097, Tables 1 & 2 from USPN 5,958,773, Table 2 from USPN 5,951,455, Table 14 from USPN 5,885,970, Tables 2 & 9 from USPN 5,877,309, Table 1 from USPN 6,046,320, Table 2 from USPN 5,962,671, Table 22 from USPN 6,133,246 and Tables 1 & 2 from USPN 6,063,626). The quantity of data existing in the scientific literature showing antisense inhibition to various target genes well illustrates that a reasonable expectation of

success exists in finding antisense to target and inhibit a target gene of known sequence by at least 42%.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO

DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JZ
12-21-04

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